# Use of an Augmented Exome for Disorders *with* High Genetic Heterogeneity

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## Introduction

### Gene Panel *vs.* Exome Test Selection Dilemma

In the testing of disorders that exhibit a high degree of genetic heterogeneity, the clinician is faced with a dilemma: whether to order a gene panel test, or to order exome sequencing? The dilemma arises due to the different ways in which causative variants can be missed through each type of test i.e. the mechanism by which the sensitivity of each test is compromised. With gene panel tests, the number of genes included in a panel for the same indication may vary widely between labs. While the analytical sensitivity for the genes included in a panel tends to be high, the *diagnostic* sensitivity of such tests can be compromised through failure to include some genes associated with the condition in a panel. In contrast, conventional exome sequencing suffers from issues of analytical sensitivity — with regions of known disease genes being poorly covered, bioinformatic errors in variant calling, reliance on an imperfect genomic reference, and interpretation through *in silico* gene panels — which in turn compromise diagnostic sensitivity.

## Methods

### Development of an Augmented Exome: The ACE Clinical Exome Test

In order to overcome the dilemma of choosing between breadth of gene coverage and comprehensive gene coverage, an augmented exome sequencing assay and bioinformatics pipeline, the ACE Clinical Exome Test, was developed. In this assay, coverage of >8000 biomedically relevant genes is enhanced, with >6000 considered "finished" (>99% of bases covered at 20x). To further improve sensitivity, the ACE Clinical Exome Test includes coverage of interpretable non-exonic regions and a sequencing-based method for genome-wide detection of structural variants. Bioinformatic approaches have been developed to address accuracy issues in variant-calling and an improved reference sequence is utilized. A phenotype-driven approach to analysis has been developed.

**FIGURE 1:** Depth Coverage Plot of *RPGR*




## Results

### Examples of Molecular Diagnoses Made with Augmented Exome That Would Have Been Missed Through Gene-Panel Testing:

### Case 1:

**Diagnosis:** Charcot-Marie-Tooth (CMT) disease type 2

**Prior Testing:** 11 genes associated with axonal CMT, negative

**ACE Clinical Exome Test Result (2014):** Two previously reported pathogenic variants, presumed in trans, in *POLG* (mother carries single variant, father not available for testing). While not generally considered a CMT-related gene, variants in *POLG* have been reported to cause a rare form of autosomal recessive CMT type 2 consistent with this patient's presentation (Lax *et al.*, Høyer *et al.*)

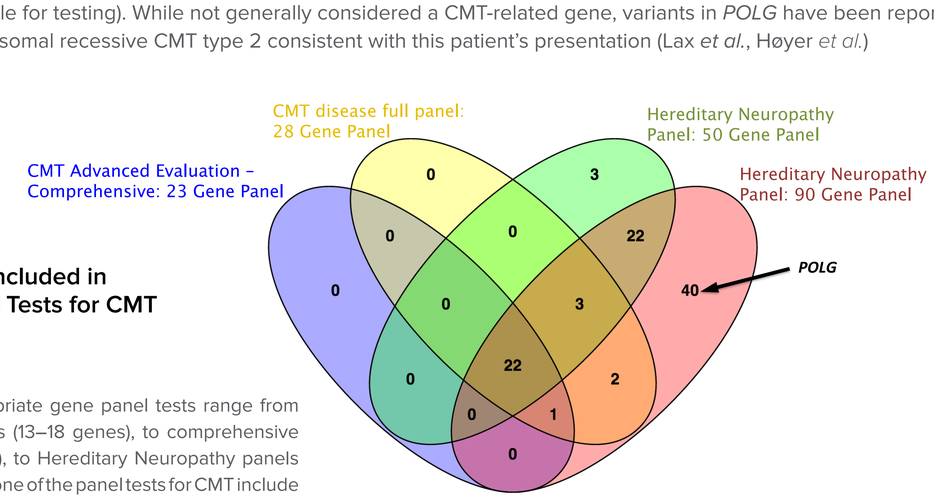


**FIGURE 2:**
**Variability of Genes Included in Available Gene Panel Tests for CMT**
(Oliveros, J.C.)

**Panel Assessment:** Appropriate gene panel tests range from axonal CMT specific panels (13–18 genes), to comprehensive CMT panels (23–49 genes), to Hereditary Neuropathy panels (50–90 genes). Currently, none of the panel tests for CMT include *POLG*, nor do some of the broader Hereditary Neuropathy panels. Searching the Genetic Test Registry and www.GeneTests.org identifies only one Hereditary Neuropathy panel test that includes *POLG*.

### Case 2:

**Diagnosis:** Leber congenital amaurosis (LCA)

**Prior Testing:** Retinitis pigmentosa/LCA gene panel

**ACE Clinical Exome Test Result (2013):** Two novel, predicted deleterious, variants in trans in *NMNAT1*.

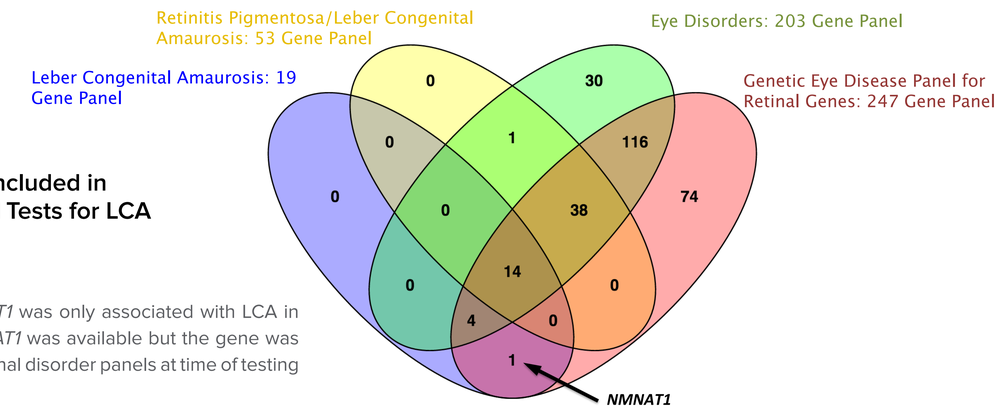


**FIGURE 3:**
**Variability of Genes Included in Available Gene Panel Tests for LCA**
(Oliveros, J.C.)

**Panel Assessment:** *NMNAT1* was only associated with LCA in 2012. Sequencing of *NMNAT1* was available but the gene was not included in any LCA/retinal disorder panels at time of testing (2013).

Revisiting this case in March 2015, the inclusion of *NMNAT1* in appropriate gene panel tests is still extremely variable despite the emergence of supportive literature: it is included in one 19-gene LCA panel, yet absent in another 18-gene panel, included in one 247-gene panel but absent from other "comprehensive" eye disorder panels ranging from 53–203 genes.

## Conclusion

### An Augmented Exome May Exhibit Higher Diagnostic Sensitivity than Gene Panels for Disorders with High Genetic Heterogeneity

Diagnoses such as those described here facilitate a retrospective analysis of the diagnostic sensitivity of gene panel tests for these patients. It is, of course, usually not possible to assess whether a particular gene panel includes the most relevant gene for a patient prior to testing. For disorders with high genetic heterogeneity, an augmented exome test, in which the issues of analytical sensitivity associated with conventional exome sequencing have been addressed, can provide diagnoses that may be missed through gene panel testing, and simplify the panel vs. exome test-selection dilemma.

**References:**

- Lax NZ, *et. al.* Sensory neuronopathy in patients harbouring recessive polymerase γ mutations. Brain. 2012 Jan 135(Pt 1):62-71.
- Høyer H, *et. al.* Genetic diagnosis of Charcot-Marie-Tooth disease in a population by next-generation sequencing. Biomed Res Int. 2014
- Oliveros, J.C. (2007-2015) Venny. An interactive tool for comparing lists with Venn's diagrams. http://bioinfogp.cnb.csic.es/tools/venny/index.html